New claims 9 and 10 are drawn to a method of inhibiting the PSC associated retrovirus using the specific composition of an antisense molecule (claim 9) or a ribozyme molecule (claim 10). Claim 9 is fully supported by the instant specification at pages 21, lines 20-37, 22, lines 1-37, 23, lines 1-37. Claim 10 is fully supported in the instant specification at pages 24, lines 25-37, 25, lines 1-30. The amendments and new claims do not represent new matter. Entry of the foregoing amendments and new claims is respectfully requested.

1. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 1-6 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention. Any informalities in the claims have been addressed in the amendments, and the rejection under 35 U.S.C. § 112, second paragraph should be withdrawn.

2. The Rejections Under 35 U.S.C. § 112,First Paragraph, Should Be Withdrawn

Claim 1, drawn to a method of identifying an individual having PSC, AIH, Crohn's disease or ulcerative colitis, and claims 3-6, drawn to a composition comprising an isolated PSC associated retrovirus, and methods of identifying or inhibiting a PSC associated retrovirus, are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention. The rejection is in error for the reasons detailed below and should be withdrawn.

The basis of the Examiner's rejection appears to be that the disclosure fails to identify members of the genus and that the genus is highly variant. The disclosure at page 37, lines 1-7 and table 3, however, points out that the disclosed cDNA sequences of PSC associated retrovirus derived from patient's bile samples do not vary. They are 98% homologous. This was true for 100% of the samples tested (3/3). Furthermore, they are clearly distinguishable from human endogenous retroviral sequences that were found in all 29 samples tested (*i.e.*, both healthy and PSC samples)(see Table 2 of the instant specification at page 36). If the Examiner is relying on any other facts within her personal knowledge as a basis for her rejection, she is hereby requested to supply an affidavit specifying with particularity the data supporting her rejection under 37 C.F.R. § 1.104(d)(2).

Since the sequences were derived by amplifying regions of the polymerase gene of retroviruses using conserved primers (page 35 of the disclosure), yet resulted in the production of unique sequences that are particular to PSC (and other auto-immune disease) patients and clearly distinguishable from known retroviruses, this indicates the presence of a novel retrovirus. It is the unique sequence and methods of using the same that are claimed in claims 1 and 3-6. The Applicants, having disclosed how to obtain and use these sequences, respectfully submit that they are indeed in possession of the invention and that the invention as claimed is disclosed and enabled by the instant specification. Thus, Applicants hereby request that the rejection of claims 1 and 3-6, based on of 35 U.S.C. § 112, first paragraph, be withdrawn.

3. The Rejections Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 5-6, drawn to a method of inhibiting replication of a PSC associated retrovirus by administering a composition which targets the PSC associated retrovirus pol sequence, are rejected under 35 U.S.C. § 112, first paragraph, for failing to describe the invention in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants submit that this rejection is in error and should be withdrawn for the reasons stated below.

Claims 5 and 6 describe the inhibition of PSC associated retrovirus. Claim 6 and newly added claim 9 describe the use of an antisense molecule. The invention as claimed is enabled. The specification particularly points out nucleic acid sequences specific to PSC associated retrovirus (page 100). It describes in detail how antisense molecules, and ribozymes, effective at inhibiting PSC associated retrovirus, might be designed (pages 21-26). The state of art is such that a skilled artisan would be able to practice the invention without undue experimentation.

The Examiner cites several factors which complicate nucleic acid-based therapies. These include the fate of the nucleic acid, itself, once administered to an individual, the *in vivo* consequences of altered gene expression and protein function, the fraction of nucleic acid taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the nucleic acid and the stability of the nucleic acid.

The *in vivo* consequences of altered gene expression does not apply in the instant case. The antisense molecules are specific and directed toward a PSC asssociated retroviral sequence. Altered gene expression is only a factor when the sequence is directed toward a portion of the endogenous genome. Because these antisense molecules are directed only

toward viral sequences no altered gene expression will occur, except for the desired alteration in viral gene expression. The teachings of Crooke concerning trafficking of genetic material, degradation, and stability of nucleic acid are all derived from *in vitro* studies. Crooke also teaches that *in vitro* studies may not, in fact, reflect what occurs *in vivo*. Crooke cites many examples of successful use of antisense therapy, including *in vivo* studies (page 26). Stability and degradation issues are addressed in the specification. The specification describes several modes of practicing the invention (page 23), including the use of a phosphothioate backbone to insure stability and efficient cellular uptake. Crooke teaches that use of a phosphorothioate creates a more stable oligonucleotide and improves cellular uptake (pages 16-18). Furthermore, Crooke teaches that phosphorothioate oligonucleotides are rapidly and extensively absorbed after parenteral administration. After an intradermal dose of 3.6 mg/kg . . . of a 20-mer phosphorothioate approximately 70% of the dose was absorbed within 4 hours and total systemic bioavailability was in excess of 90%. After intradermal injection in man absorption of ISIS 2105 was similar to that observed in rat (page 17).

Crooke teaches that the therapeutic use of antisense molecules is, in fact, known in the art. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation from the disclosure in the patent specification, coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). Enablement is not precluded, even if some experimentation is necessary. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). The need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112.

This is so even if the amount of experimentation is laborious. *In re Wands*, 858 F.2d 721 (Fed. Cir. 1988).

The Applicants assert that, in view of the teachings in the specification concerning design of antisense and ribozyme molecules, together with the state of the art as described in the literature cited in the specification, the invention is fully enabled such that a skilled artisan could practice the same without undue experimentation. The Applicants, therefore, respectfully request that the rejection of claims 5-6 pursuant to 35 U.S.C. § 112, first paragraph be withdrawn.

4. The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

Claim 1, which is drawn to a method of identifying an individual having PSC, AIH, Crohn's disease, or ulcerative colitis, is rejected under 35 U.S.C. § 103 as obvious over Mason *et al.* ("Mason") in view of Peterson *et al.* ("Peterson"). The rejection is in error and should be withdrawn for the reasons detailed below.

The Examiner contends that the cited art makes obvious the novel virus and viral sequences and methods of detection of the present invention. Nothing in either Mason or Peterson suggests the unique sequence associated with a PSC retrovirus which the Applicants have disclosed in their specification and is the subject matter of claim 1. While Peterson does describe sequences specific to HIV and methods of detecting HIV infection, nowhere is it stated or suggested in either reference that any shared homology exists between the disclosed unique PSC associated retroviral sequences of the present invention and the HIV related sequences disclosed in Peterson.

An obviousness rejection requires inquiry regarding the scope and content of the prior art, the differences between the prior art and claims at issue, and the level of ordinary skill in the art. *Graham v. John Deere,* 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell,* 853 F.2d 894, 903 (Fed Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicant's disclosure. *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991).

In the present instance, the relevant inquiry is whether a novel retrovirus associated with primary schlerosing cholangitis would be obvious to one of ordinary skill in the art, in view of Peterson which describes sequences specific for HIV, and Mason which describes cross reactivity between serum taken from patients suffering from Primary Biliary Cirrhosis and p24 of HIV. The Applicants assert that there is no connection between the claimed invention and the cited references.

The Examiner correctly points out that Mason does not teach a method for detecting the presence or absence of a nucleic acid molecule of a virus associated with PSC. The Applicants invite the Examiner's attention to the fact that Mason refers to PBC (Primary Biliary Cirrhosis), which is distinct from PSC (Primary Schlerosing Cholangitis). Mason does not teach any methodology for identifying an individual having PSC, AIH, Crohn's disease or ulcerative colitis. It merely demonstrates that serum taken from PBC (emphasis added) patients cross-reacts with p24 of HIV or p61 of HIAP. The authors suggest, without concluding, that this result may indicate that the etiological agent of PBC is a retrovirus or alternatively, PBC patients have autoimmune antibodies that happen to cross-

react with some retroviral proteins. No conclusion regarding these alternative hypotheses is reached by Mason. It is therefore inappropriate to assume the data suggest that the etiological agent of PSC, or the other autoimmune diseases mentioned, is a retrovirus. Thus, a skilled artisan would not have a reasonable expectation of success in the development of a method to detect a unique PSC associated retrovirus.

Mason indicates that PSC patients (39%) had sera that also cross-reacted with HIV p24 (table 1). The observation is presented (along with data points concerning other auto-immune diseases) as a control for the PBC experimental data. Mason does not specify a method for identifying PSC patients, after all 61% of the PSC samples tested failed to cross react with the HIV antibody. The authors propose, without concluding that the observed cross reactivity may be the result of the presence of an unique retrovirus. The mere fact that some PSC patients have an antibody that cross-reacts with a different retrovirus can hardly be considered to be a "method of identifying individuals with PSC," particularly when the majority of patient's samples do not cross react.

Peterson teaches a method for detection of HIV by oligonucleotide hybridization and a method of amplifying HIV-specific nucleic acid through the design of specific primers. Nothing in Peterson suggests that these sequences would be effective in recognizing PSC associated retroviral sequences. In fact the unique sequences disclosed in the instant application suggests that they might not be effective.

Furthermore, the Applicant respectfully submits that Mason does not provide a direct link between the presence of PSC in an individual and HIV-1 infection. Since nothing in either Mason or Peterson, or the combination of these references would suggest the unique sequence of the PSC associated retrovirus, or a method of detecting the same,

the Applicants respectfully request that the obviousness rejection of claim 1, pursuant to 35 U.S.C. § 103, be withdrawn.

5. The Rejections Under 35 U.S.C. § 102(e) Should Be Withdrawn

Claims 3-4 are rejected under 35 U.S.C. § 102(e) as anticipated by Peterson (U.S. Patent No. 5,919,701) in view of Mason. Claim 3 is drawn to a composition comprising an isolated PSC associated retrovirus. Claim 4 is drawn to a method of identifying an individual infected with a PSC associated retrovirus comprising the step of detecting the presence of a PSC associated retroviral nucleic acid molecule. This rejection is in error and should be withdrawn for the reasons detailed below.

The legal test for anticipation under 35 U.S.C. §102 requires that the prior art meet every element of the claimed invention, and such a determination is one of fact. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986) *cert. denied*, 480 U.S. 947 (1987). Anticipation under 35 U.S.C. §102 requires identity of invention. *Scripps Clinic & Research Fdn. v. Genetech Inc.*, 927 F.2d 1565 (Fed. Cir. 1991). Anticipation under 35 U.S.C. §102 also requires that the prior art reference places the claimed invention in the possession of the public through an enabling disclosure. *Charles v. Miller,* 906 F.2d 1574, 15 U.S.P.Q. 2d 133 (Fed. Cir. 1990).

The Peterson reference does not meet the requirement of anticipation of the claimed invention. As the Examiner correctly points out, Peterson discloses a method for the detection of HIV nucleic acid and compositions comprising the HIV virus. Peterson does not describe a PSC associated retrovirus nor does it describe methods of identifying individuals infected with a PSC associated retrovirus. Furthermore, Peterson does not

describe PSC associated retroviral nucleic acid molecules. Instead, Peterson describes a method for detection of HIV nucleic acid, not PSC associated retroviral nucleic acid molecules. Thus anticipation cannot be found as Peterson does not describe the PSC associated virus or the associated nucleic acids of the present invention, hence the rejection of claims 3-4 under § 102(e) should be withdrawn.

The Examiner states that according to Mason, HIV is a PSC associated retrovirus. Nowhere in Mason is it implied, stated or in any way suggested that HIV-1 is a PSC-associated retrovirus. The authors clearly state that their results could imply the existence of an autoimmune disease associated retrovirus or that patients suffering from some autoimmune diseases happen to have antibodies that cross react with one protein found in HIV-1 and HIAP. The authors emphatically state that none of these patients were infected with HIV, (Results page 1621) hence there is no basis to conclude that HIV is a PSC associated retrovirus. Even assuming *arguendo*, that Mason did state this (and it clearly does not), a 35 U.S.C. § 102(e) rejection would still be inappropriate because it would require combining both the Peterson and Mason references.

Thus the invention of claims 3-4 is not anticipated, and therefore, the Applicant respectfully requests that the rejections under 35 U.S.C. § 102(e) be withdrawn.

CONCLUSION

Applicant respectfully requests entry and consideration of the foregoing amendments and remarks. No new matter has been introduced. The claims are believed to be free of the art and patentable. Withdrawal of all of the rejections and an early allowance is earnestly sought.

Respectfully submitted,

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